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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/749,119	12/30/2003	Richard L. Boyd	286336.152US1/NOR-013CP2	3286

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WILMERHALE/BOSTON
60 STATE STREET
BOSTON, MA 02109

EXAMINER
LI, QIAN JANICE

ART UNIT	PAPER NUMBER
1633	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

michael.mathewson@wilmerhale.com
teresa.carvalho@wilmerhale.com
sharon.matthews@wilmerhale.com

Office Action Summary	Application No.	Applicant(s)	
	10/749,119	BOYD, RICHARD L.	
	Examiner	Art Unit	
	Q. JANICE LI, M.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-26,28-40,42-44,46-49,53,55-64 and 66-75* is/are pending in the application.

4a) Of the above claim(s) *21, 22, 24, 26, 32, 33, 37, 44, 53, 56, 61, 63, 67, 71-75* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19,20,23,25,28-31,34-36,38-40,42,43,46-49,55,57-60,62,64,66 and 68-70* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment and remarks filed 4/17/08 are acknowledged. Claims 19, 35, 36, 42, 66, 69 have been amended. Claim 65 has been canceled. Claims 19-26, 28-40, 42-44, 46-49, 53, 55-64, 66-75 are pending, however, claims 21, 22, 24, 26, 32, 33, 37, 44, 53, 56, 61, 63, 67, 71-75 are withdrawn from further consideration by the Examiner, pursuant to 37 CFR 1.142(b), as being drawn to non-elected inventions, there being no allowable generic or linking claim. Claims 19, 20, 23, 25, 28-31, 34-36, 38-40, 42, 43, 46-49, 55, 57-60, 62, 64, 66, 68-70 are under current examination.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment to pending claims will not be reiterated. The arguments in 4/17/08 response would be addressed to the extent that they apply to current rejection.

Election/Restrictions

Applicant's election with traverse of Group I, is acknowledged. The elected invention is drawn to a method of inducing graft tolerance in a patient, and species election drawn to a combination of the following: depleting T cells with chemotherapy before thymus reactivation in a post-puberty patient, reactivate thymus with leuprolide, and administering hematopoitic cells to inducing tolerance to an allogenic organ/tissue. Upon further consideration, group IV,(claims 69, 70) has been rejoined with group I, and the restriction between groups IV and I is hereby withdrawn. Claims 19, 20, 23, 25, 28-31, 34-36, 38-40, 42, 43, 46-49, 55, 57-60, 62, 64-66, 68-70 read on the elected invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 19, 20, 23, 25, 28-31, 34-36, 38-40, 42, 43, 46-49, 55, 57-60, 62, 64, 66, 68-70 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for increasing tolerance in a patient to a graft from a MHC-mismatched donor, wherein the graft is the allogeneic hemopoietic or mesenchymal stem cell, does not reasonably provide enablement for increasing tolerance in a patient to another MHC-mismatched graft. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims, for reasons of record and following.

The amended claims are directed to inducing tolerance to a graft from a mismatched donor via the steps of a) T cell depletion/immune suppression, b) reactivation of thymus of the recipient, c) administering stem cells, and d) providing the graft from the MHC-mismatched donor to the patient.

In the remarks, the applicant provides a post-filing publication from the applicant to support the claimed invention. The argument and the Goldberg publication have been fully considered, but they fail to support instant claims for reasons below.

The *Goldberg* publication reduced to practice showing that surgical castration promoted hematopoietic and T cell recovery following allogenic HSC transplantation (step c of instant claims), and increased cell numbers in bone marrow and thymus. However, the publication does not further test the tolerance to another graft, and thus it fails to support that the manipulation of steps a) to c) increased tolerance to another

allogenic graft. To the contrary, when testing the graft-vs-tumor activity, the publication shows there is no change of host response to another graft (tumor) following the allogenic HSCT. "MORTALITY DUE TO MASTOCYTOMA REMAINED UNCHANGED FOLLOWING CASTRATION (SIX OF NINE MICE) WHEN COMPARED WITH SHAM-CX CONTROLS (FIVE OF EIGHT MCIE). THIS SUGGESTS THAT CASTRATION DOES NOT DIMINISH GVT RESPONSE FOLLOWING HSCT (FIG. 5A)" (Column 1, page 7479).

This observation apparently is consistent with the cited art of record as taught by *Takami et al* (J Heart Lung Transplant 1995;14:529-36), who teach orchiectomy (activating thymus through castration) had no influence on graft survival time or grade of rejection (e.g. the abstract); *Schofield et al* (J Heart Lung Transplant 2002;21:493-5), who reported that the leuprolide hormone therapy appears to increase the risk of cardiac allograft rejection; *Antus et al* (Transpl Int 2002;15:494-501), who teach testosterone treatment increases graft rejection while estrogens reduced the degree of graft rejection. It is particularly noteworthy that *Sykes et al* (US 2002/0159999) teach in the context of inducing graft tolerance the steps of immune suppression or T cell depletion, and administration of hematopoietic stem cells, while thymus is deactivated by radiation to “make space” for the stem cell transplantation. The specification and the post-filing publication only supports an enhanced recovery of the allogenic hematopoietic cells (of step c), not increased tolerance to another graft (instant step d).

Therefore, in view of the limited guidance, the lack of predictability of the art and the breadth of the claims, one skill in the art could not practice the invention without undue experimentation as it is broadly claimed.

The following prior art rejection applied even though they don't provide *another* "graft from the MHC-mismatched donor to the patient" in addition to the allogenic HSCs. However, given the broadest reasonable interpretation, the allogenic HSCs could be considered as "the graft from the MHC-mismatched donor". Moreover, the claimed invention relies on the results from experiments, wherein only the first three steps were performed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 19, 20, 23, 25, 28-31, 34-36, 42, 43, 46, 55, 57-59, 62, 64, 66, 68-70 stand rejected under 35 U.S.C. 103(a) as being obvious by *Ghalie et al* (Am J Hematol 1993;42:350-3).

Ghalie et al teach a method comprising ablating the patient's T cells by total body irradiation and cyclophosphamide chemotherapy (Patient Characteristics, page 361), reactivating the patient's thymus by administering LHRH agonist leuprolide intravenously or orally in a pharmaceutical composition before, at the time, or after receiving donor cells (Leuprolide Administration, page 361), which would reactivate

thymus through disruption of sex steroid-mediated signaling to the thymus; wherein the patients are post-pubertal (median age 26), wherein the patients had chemotherapy or radiation therapy (minor or full myeloablation), received autologous and allogeneic (MHC-mismatched) bone marrow transplantation respectively, which BM contains CD34+ HSCs, and hence the patient would have an increased tolerance to a graft compared to an untreated donor. *Ghalie et al* use an LHRH analog, and hematopoietic stem cells (kit) for treatment. Accordingly, *Ghalie et al* anticipate instant claims.

In the remarks, the applicant argues that Ghalie et al do not provide each and every element of the claimed invention, particularly administering cells from the MHC-mismatched donor and providing the graft from the MHC-mismatched donor.

In response, the allogenic bone marrow transplantation disclosed by *Ghalie et al* meets the limitation of administering cells from the MHC-mismatched donor as well as providing the graft from the MHC-mismatched donor. Since *Ghalie et al* discloses each and every step of the claims, it antipates instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 19, 20, 23, 25, 28-31, 34-36, 38-40, 42, 43, 46-49, 55, 57-60, 62, 64, 66, 68-70 stand rejected under 35 U.S.C. 103(a) as being unpatentable over *Mardiney, III et al* (USP 6,863,885), in view of the BBC News (December 1998), and *Windmill et al* (Tissue Cell. 1998;30:104-11).

Mardiney III et al teach a method for allogenic (mismatched donor) graft (inducing tolerance to a graft) comprising administering hematopoietic growth factors and cytokines, ablating the patient's T cells by non-myeloablative dose of radiation or chemotherapy, followed by hematopoietic stem cell transplantation. *Mardiney III et al* teach the radiation eradicates diseased blood cells, while the growth factor promotes the regeneration of new blood cells (e.g. column 3). *Mardiney III et al* established the state of the art with respect to inducing tolerance to allogenic grafts, which is a pre-conditioning regimen that includes either high dose radiation/chemotherapy or a lower dose non-myeloablative regimen accompanied by hematopieitic growth factors and cytokines (e.g. claims). *Mardiney III et al* go on to teach the goal of a pre-conditioning regimen is to eliminate diseased cells such as leukemia/lymphoma, to create an environment in the recipient in which the donor's HPCs can successfully engraft by homing into the recipient's bone marrow to further undergo hematopoiesis, and serve as an immunosuppressive agent to mitigate graft rejection in the treatment of non-cancerous diseases (e.g. column 1). *Mardiney III, et al* do not teach using thymus reactivation in the transplantation procedure.

The cited BBC News supplemented the deficiency by establishing it was known in the art that chemical castration via sex hormones can restore/regenerate thymus

function and thus be used at the time of transplantation to promote the recovery of immunosuppressed recipient. Although the News did not give details about castration and thymus regeneration, the teaching of *Windmill et al* evidenced that it was known in the art before the instant priority date, castration could increase the weight of thymus, as well as the numbers and responsiveness of T cells in peripheral blood (e.g. abstract), and it was also known in the art sex hormones are closely interrelated with thymus function and immune system (Introduction and Discussion).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method taught by *Mardiney, III et al*, by combining the chemical or surgical castration in a transplantation protocol with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to do so for added benefit of restoring the recipient hemotopoietic system or in complex clinical cases, where additional measurement to ensure the success of stem cell transplantation is required. Although the combined teachings do not specify a kit or the LHRH antagonists known in the art, it would have been obvious to the skilled in the art to assemble a kit containing active ingredients to be used in the combined therapy for the ease of commercial activity. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

In the remarks, the applicant argues that the combined teachings do not provide all of the claim limitations, particularly administering cells from the MHC-mismatched donor and providing the graft from the MHC-mismatched donor.

In response, the allogenic bone marrow transplantation disclosed by *Mardiney III et al* meets the limitation of administering cells from the MHC-mismatched donor as well as providing the graft from the MHC-mismatched donor. Further, since the cited BBC News establishes it was known in the art that chemical castration via sex hormones can restore/regenerate thymus function and useful for patients to accept transplanted organs, it would have suggested to the skilled artisan to use such in organ/tissue transplantation.

Accordingly, for reasons of record and set forth supra, the rejection stands.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is **571-272-0730**. The examiner can normally be reached on 9:30 am - 7 p.m., Monday through Friday, except every other Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The **fax** numbers for the organization where this application or proceeding is assigned are **571-273-8300**.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

For all other customer support, please call the USPTO Call Center (UCC) at **800-786-9199**.

/Q. JANICE LI, M.D./

Primary Examiner, Art Unit 1633

Q. Janice Li, M.D.
Primary Examiner
Art Unit 1633

QJL

July 10, 2008